DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/11/09 has been entered.

Election/Restrictions

Applicants' election with traverse of the species of tetrapeptide substrate sequence P4-P1 that is Phe-Ser-Phe-Asp (FSFD) and the species of disease that is an apoptosis-mediated disorder, which is an ischemic injury in the reply filed on 10/01/09 is acknowledged. The traversal is on the ground(s) that in the Requirement for Restriction and Election mailed November 02, 2004, the Office already has previously issued an Election of Species requiring election among different species. In the response thereto, mailed January 03, 2005. Applicant elected the species of A) N is a positive integer between 1-20; B) the granzyme B as the protease scaffold; and C) cancer as the pathology. The Office also issued an Election of Species in the

Requirement and Election mailed April 11, 2006. In the response thereto, mailed September 11, 2006, Applicant elected the species of target protein that is caspase 3 and the species of protease that is granzyme B. The instant Election of Species, requiring further election of a tetrapeptide substrate sequence and a disease, is improper insofar as this election is not mutually exclusive from the prior election, since election of a target protein constrains the particular substrate sequence as well as the diseases. Thus, selection among each choice could result in election of a plurality of species, in addition to the species already elected. This is because the target protein or substrate in a target protein is one that is involved with a disease or pathology. Hence, the disease is one in which the target protein is involved. Further, the tetrapeptide substrate sequence is a sequence in the target protein. Hence, the tetrapeptide sequence also is a sequence in the target protein. The Examiner, however, has not limited the Election of Species requirement to species elected in the previous Election of Species. Thus, Applicant could elect a disease and tetrapeptide substrate that are not related to the target protein caspase 3 previously elected. Hence, the election as set forth can result in election of several species. Since election of previous species of target protein of caspase 3 fixes the choice of

election of species herein, it is redundant with the previous election of target protein. Thus, the election of the previous species is sufficient for search purposes.

In view of applicants' traversal above, the species with respect to the tetrapeptide sequence is withdrawn and also the disease since as applicants state election of species is redundant with the previous election of target protein.

Status of Claims

Claims 1-7, 9, 11-16, 45, 48, 50-54, 56-59, 61-63 and 65-78 are pending and under examination in the application.

Withdrawn Rejection

In view of the amendments to the claims and applicants' arguments the 35 USC 103 rejections over Koltermann and Harris et al (I or II), alone have been withdrawn.

Information Disclosure Statement

The information disclosure statement filed on 10/1/09 (filed as a transmittal letter) fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the list of other information i.e., copy of examination report from Australia and New Zealand submitted for consideration is not listed in a section separately from citations of other documents. It has been placed in the application file, but the information referred to therein has not been considered as to

the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9, 11-16, 45, 48, 50-54, 56-59, 61-63 and 65-78, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter Rejection

Claim 1 which recites "inactivation can **ameliorate** a disease or pathology" is not supported in the as-filed specification. MPEP 714.02 clearly states that applicants point out where support can be found for the new claim limitations. The amendments to the claims filed on 6/11/09 contain numerous changes. It is requested that applicants point out the sections for each of the specific amendments made in the claims. It is not readily apparent from the given paragraphs which amendments find support therein. The claim to "a **polypeptide** comprising a substrate sequence..." is also not in the original disclosure. The original disclosure cited by applicants at e.g., paragraphs [0050] and [0125] do not recite a polypeptide rather the protein per se with the substrate sequence. Thus, it is not apparent as to the residues, length or location of the polypeptide relative to the protein. Furthermore, the support for the protease scaffold "and catalytically active **portions** thereof" is not provided in any of the paragraph sections cited by applicants for support.

Written Description Requirement

For claims 1-7, 9, 11-16, 45, 48, 50-54, 56-59, 61-63 and 65-78, as amended, the specification fails to provide a written description for a candidate protease mutein that inactivates an activity of a target protein the inactivation of which can

ameliorate a disease or pathology. The general statements in the specification are not a detail description of the invention. The Examples do not disclose candidate protease mutants that ameliorate any kind of diseases such as the claim any cancer disease or AIDS (HIV). The detail description provided in Example 8 of the instant specification describes a method of cleaving the different proteins e.g., TNF, VEGR **involved** in different disease or pathologies. The cleaving enzyme or protein however, has not been shown to be effective in the treatment of the variously claim disease(s). None of the description in the Example describes a disease that has been treated by the candidate enzyme. The specification simply recites the involvement of the specific target protein to the different diseases due to the cleavage of the substrate protein. There is no description as to the candidate protein being useful to treat the disease of at times unknown etiology as cancer or for any types of cancer. In this regard attention is drawn to the newly submitted prior art, Trapani (Genome Biology, 2001) at e.g., page 6, last paragraph which discloses that despite their biological importance, granzymes are still relatively poorly studied and many important questions remain to be answered. The nature of the synergy between perforin and granzyme - that is, the mechanism by which granzymes are released from the target

cell's endosomes - remains poorly understood. Caspase-independent cell-death pathways are very important, because they allow CTLs to kill cells in which caspases have been blocked by viral inhibitors, such as the cytokine response modifier A (crmA) expressed by poxviruses. Again, the nature of these pathways has not been elucidated. Granzymes other than A and B doubtless have many functions other than in apoptosis, and the generation of further gene knockout mice should help to cast light on this area of research. It will also be fascinating to learn more about the regulation of granzyme function mediated by novel serpins. These studies could have major implications for our understanding of immune homeostasis (for example, the regulation of CTL numbers following an infection), and of effector responses to viral disease and cancer.

For claims 1-7, 9, 11-16, 45, 48, 50-54, 56-59, 61-63 and 65-78, as amended, are rejected for lacking written description. The specification describes granzyme as the sole cleaving enzyme used in the method. Claim 1, for example, encompass an enormous variation of enzyme muteins, even for granzyme alone which contain numerous allelic variants. It is not known how many allelic variants of granzyme, let alone of the huge protease exist and what the structures even look like for each of any proteases. Thus, the genus of proteases encompassed by the

claims as employed in the method is too large and structurally diverse. However, the specification only describes a single species of this genus e.g., granzyme, with particularity but these species are not deemed as representative of said genus. It is noted that the MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated: "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents" of the University of California v. Eli

Lilly & Co., 43 USPQ2d 1398. Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co. the court stated: "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Fiefs, 984 F.2d at 1171, 25 USPQ2d 1601; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398. In addition, it is noted further that the Court has held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of which peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. See University of Rochester v. G.D. Searle & Co., Inc., 69 USPQ2d

1886,1895 (Fed. Cir. 2004). It is asserted, however, that the instant claims are not adequately described in the specification to claim the broad and structurally diverse genus of the compounds use in the method. The claims lack written description and a skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus that are allelic variants. This is true even for the single granzyme, let alone for any enzymes of no claim distinguishing features as use in the broad method steps. The method steps broadly comprises the steps of producing any library of protease mutein, contacting and measuring any cleavage activity of any enzyme at any sites for any kind of target protein. At the time of applicants' invention it is known that in biotechnology art one species cannot be extrapolated to another due to the numerous unforeseeable reaction or interactions of protease-substrate. For example, Rosen et al (20020086811) discloses at e.g., paragraph [0018] that caspases are among the most specific of proteases, with an unusual and absolute requirement for cleavage after aspartic acid. (The only other eukaryotic protease known to have a similar specificity is the serine protease granzyme B, a mediator of granule-dependent cytotoxic T lymphocyte-mediated apoptosis). Recognition of at least four amino acids NH2-terminal to the cleavage site is also

a necessary requirement for efficient catalysis. The preferred tetrapeptide recognition motif differs significantly among caspases and explains the diversity of their biological functions. Their specificity is even more stringent: not all proteins that contain the optimal tetrapeptide sequence are cleaved, implying that tertiary structural elements may influence **substrate** recognition. **Cleavage** of proteins by **caspases** is not only specific, but also highly efficient. The strict specificity of caspases is consistent with the observation that apoptosis is not accompanied by indiscriminate protein digestion; rather, a select set of proteins is **cleaved** in a coordinated manner, usually at a single site, resulting in a loss or change in function.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9, 11-16, 45, 48, 50-54, 56-59, 61-63 and 65-78, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 1, 53, 59 and 63, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. This claim is an omnibus type claim. It claims a method of producing and identifying a mammalian protease that inactivates an activity of a target protein involved with ay disease or pathology. Screening a candidate protease, selection of a target protein from among that claim that is involved in any of the claim disease and treatment of any of the diseases by the screened and identified enzyme.

2. Claims 1, 53, 59 and 63 are vague and indefinite as to the differentiating features of a disease or pathology in a mammal that is ameliorated by an inactivation of a target protein involved in said disease or pathology.

3. In claims 1, 53, 59 and 63, the metes and bound of the "catalytically active **portions**" or a protease **scaffold** is not clearly set forth in the specification and claims. It is not clear as to the basis or location by which a portion of a scaffold is considered to be its "catalytically active portions", especially in the absence of positive support for the infinite mammalian protease as claimed.

4. In claims 1, 53, 59 and 63 the definition of N as a positive integer is infinite and does not circumscribe the claim

mutations with particularity in claiming for any kind of residue(s) mutation at any locations or of any length.

5. Claims 1, 53, 59 and 63, as amended, is vague and indefinite with respect to step b) recitation that the members of the library is contacted with a polypeptide comprising a substrate sequence that is present in the target protein. There are no differentiating features of a protein from a polypeptide or a polypeptide comprised in a protein containing a substrate sequence.

6. Claims 1, 53, 59 and 63, as amended, are vague and indianite in step (d) recitation of "based on the measured activity and/or specificity" as to the kind of activity or the apparent specificity that can be measured from a protease mutant. Further, it is unclear as to how the identified protease is considered to be a "candidate" for treatment of any of disease or pathology. The term "candidate" is a relative term. It is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. One may consider one enzyme to be a candidate while another may not.

Claim Objections

Claim 66 is objected to because it depends upon cancelled claim 64. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 9, 11-16, 45, 48, 50-54, 56-59, 61-63 and 65-78, as amended, are rejected under 35 U.S.C. 102(b) as being anticipated by Lien et al(Combinatorial Chemistry and High Throughput Screening, 1999)(as evidenced by Shi et al, USP 20020197701).

For claims 1-7, 13, 16, 45, 50-54, 57-59, 61 and 67-78, Lien discloses at e.g., pages 73-75 a method of identifying serine proteases using targeted combinatorial mutagenesis of serine proteases with N mutations (e.g., Fig. 1, page 74). The method comprises producing sizeable libraries of mutant enzymes (N mutations), contacting the library with a substrate and identifying the mutant. Screening and selecting methods both depend not only on the activity and specificity of mutant

proteins but also on their individual expression levels (e.g., page 77, col. 1, first complete paragraph). Lien discloses at e.g., page 77, first incomplete paragraph, quantitative assessments of cleavage made by monitoring the hydrolysis (inactivation as claim) of a set of synthetic peptides esters in a colorimetric plate assay. Lien discloses at e.g., page 73 that the mutant enzyme is useful for therapy as in blood coagulation.

For claim 13, Lien discloses mutants with improved cleavage of at least 62.

For Claim 56, Lien discloses that phage displayed proteins can be subjected to in vitro selection procedures, e.g., page 77, first incomplete paragraph, col. 1.

For claims 16, 45, 57, Lien discloses at e.g., page 74, chemical mutagenesis, passage through bacterial mutator strains and PCR. (See also e.g., paragraph bridging pages 76-77.)

For claim 52 Lien discloses at e.g., page 76, col. 2 "in vivo" selection.

For claim 61, Lien discloses at e.g., page 86, col. 2, first incomplete paragraph, granzyme B.

For claims 69, 72, 75 and 78, Lien et al discloses at e.g., page 76, col. 2, and last incomplete paragraph chromogenic substrates.

For claims 68, 71, 74 and 77 Lien discloses at e.g., page 78, col. 1-col.2, under Screening Methods, tetrapeptide with P1=Phe.

The claim inactivation of a target protein involved with a disease or pathology in a mammal that ameliorate a disease is a property inherent or implicit to the teachings of Lien. [This is evident from the teachings of Shi et al at e.g., paragraph [0003]. Shi states that members of the serine **protease** family which play important roles in a range of cellular functions and which have demonstrated causative roles in human **diseases** include tissue-type plasminogen activator and thrombin (thrombosis and blood clotting), urokinase-type plasminogen activator (cancer and metastasis), trypsin and elastase (emphysema and liver **disease**) and angiotensin converting **enzyme** (hypertension).

Claims 1-5, 7, 9, 11, 13-16, 48, 50-54, 58-59, 61-63, 65 and 67, as amended, are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Guinto et al (Proc. Natl. Acad. Sci. USA, 96, pp. 1852-1857, March 1999).

Guinto et al discloses at e.g., page 1852, Materials and methods heading up to page 1853, including fig. 1 and fig. 2 a method of identifying a mammalian protease by providing from a

database a total of 284 enzymes including enzymes involved in degradation (trypsin, chymotrypsin, and elastase), fibrinolysis (plasmin, tissue plasminogen activator, and urokinase), cellular-mediated immunity (granzymes and mast cell proteases), embryonic development (Easter and Snake), the vitamin K-dependent enzymes of blood coagulation (thrombin, factor Xa, factor IXa, and activated protein C) and complement proteases (C1r, Cls, MASP-I, and MASP-2). The variability of residue 225 in coagulation factor Vlla is analyzed. Guinto at e.g., page 1854, col. 2, provide mutants which are contacted with chromogenic and natural substrates such as fibrinogen, protein c and antithormbin III. It was found that the nature of residue 225 influences the catalytic activity of the enzyme up to 8,000-fold (Fig. 2). Mutants (N, as claim) with Tyr and Phe are associated with the highest specificity. The ability to interact with the natural inhibitor antithrombin III follows the same pattern as the other ligands and is compromised up to 60,000-fold in the Ile mutant. The similarity of the activity profiles in Fig. 2 suggests that the nature of residue 225 influences a structural domain recognized by small chromogenic substrates, natural substrates, and inhibitors alike.

The claim ability of the candidate mutant as a therapeutic for treatment of the disease associated with the target

substrate is a property considered inherent to the prior art mutant serine proteases. The ability of the mutant protease to catalyze the target protein such as fibrinogen or protein C will result in the inactivation of the target hence its amelioration of the disease associated with fibrinogen or protein C. Furthermore, the claim function of the target protein e.g., a signaling protein that regulates apoptosis is a function inherent to the prior art target protein.

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same..." The burden of proof is similar to that required with respect to product-by-process claims. In re Fitzgerald, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)). See MPEP 2112.

Claim Rejections - 35 USC § 103

Claims 1-7, 9, 11-16, 45, 48, 50-54, 56-59, 61-63 and 65-78, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Lien et al in view of either Harris et al (The

Journal of Biological Chemistry)(I) or (Current Opinion in Chemical Biology(II) and Waugh et al (Nature Structure Biology).

Lien is discussed supra. Lien does not disclose the enzyme as granzyme (albeit suggests said granzyme, above) and the substrate as caspase (elected species).

Harris et al discloses at page 27364, identification of in vivo targets of granzyme B based on the elucidation of the substrate specificity of granzyme B. For example, Harris et al. teaches that based on the substrate specificity of granzyme B, certain caspases (caspases 3 and 7), based on their sequences, are more likely substrates then other caspases. Harris et al., also teaches that based on the sequence specificity of granzyme B, nuclear lamin A and nuclear poly(ADP)ribose polymerase (PARP) are potential in vivo substrates for granzyme B. Harris et al. I also teaches that amino acid position Arginine 192 is a structural determinant of specificity of granzyme B, since granzyme B mutations R192E and R192A exhibit reduced hydrolysis of the optimal tetrapeptide substrate Ac-IEPD-AMC and non-optimal tetrapeptide substrate Ac-IKPD-AMC compared to the wild-type enzyme. Harris also discloses at e.g., pages 27372 up to and 27373:

> ….{T]here is a functional relationship between the preferential substrate sequence of granzyme B and the activation site of members of the caspases (Fig. 5D).

> Indeed, studies have shown that granzyme B cleaves and activates several **caspases involved in apoptosis.** Our data on the substrate specificity of granzyme B suggest that caspase 3 and caspase 7 are preferentially activated during apoptosis. Knowledge of the extended substrate specificity of granzyme B allows for the proposal of additional targets of granzyme B during apoptosis. The substrate specificity of caspase 6 matches that of granzyme B, suggesting that both enzymes cleave the same substrates. Several proteins known to be cleaved during apoptosis, such as nuclear lamin A….
> The identification of their specificity will further expand our knowledge of the role that granzymes play in **cytotoxic, lymphocyte-mediated cell death.**

Harris (II) throughout the article, at e.g., pages 127-129, basically discloses the same method as Harris (I).

Waugh discloses at page 762 that granzymes are a vital component of the cytotoxic lymphocyte's ability to induce apoptosis, contributing to rapid cell death of a tumor or virally infected target cell by the cleavage of downstream substrates and the activating cleavage of caspases.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use as the serine protease granzyme in the method of Lien. Harris teaches that granzyme is a substrate for caspases or caspases can act as substrate depending on its sequence. Accordingly, one would have a reasonable expectation of success in using other serine protease, such as granzyme as taught by Lien as the other serine proteases. Furthermore, one would also have a reasonable

expectation of success in using granzyme as an enzyme for caspase substrate depending upon the sequence contain in each enzyme as taught by Harris above. One would be motivated to use either caspase or granzyme to act as enzyme or substrate due to the dual role each enzymes exhibits depending upon the sequence that is contained therein. Furthermore, caspase and granzyme are only the two most specific of proteases, with an unusual and absolute requirement for cleavage after aspartic acid.

Applicants'' arguments with regards to the 35 USC 103 rejections over Harris references, alone in the REMARKS filed on 6/11/09 are moot in view of the new grounds of rejection supra.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or

provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7, 9, 11-16, 45, 48, 50-54, 56-59, 61-63 and 65-78, as amended, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, for example, of copending Application No. 12/005949 ('949 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claim method is similar, if not nearly identical to the method of the '949 application. The subject matter of the instant and the '949 applications overlap in scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No claim is allowed.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Halenbeck (5843693) describes methods and compositions for a purified polypeptide comprising the pro-form of a granzyme having an N-terminal amino acid sequence of X-E, wherein X represents a variable amino acid and wherein E represents glutamic acid and wherein said N-terminal sequence renders the granzyme catalytically inactive and wherein the granzyme when active catalyzes the cleavage of a membrane bound protein hormone or receptor ligand to generate the free, soluble form of the ligand.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TERESA WESSENDORF/
Primary Examiner, Art Unit 1639